# Workshop on FVIII Inhibitors in PTP's

## Proposal for Prospective Pharmacosurveillance

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**Workshop on FVIII Inhibitors**
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# Workshop on FVIII Inhibitors in PTP's

## The Question: Host or Product?

**Post-Licensure Pharmacosurveillance**

- **Will pre-licensure clinical trials have the power to ascertain true PTP inhibitor incidence?**

**or**

- **Will a post-licensure pharmacosurveillance program be required?**

# Why Pharmacosurveillance?

- Post-marketing pharmacovigilance recognized by industry / regulatory organization as important to identification of **ongoing safety / efficacy concerns** and **redefining risk / benefit ratios.**[1]
- Currently, **"mandatory" spontaneous AE reporting** of clinical safety / efficacy concerns is primary method of surveillance.

1. Talbot JCC and Nilsson BS. Br J of Clin Pharmacol, 1998.

# Spontaneous AE Reporting

## Important Function

- Alerts physicians / regulators / industry to
  - early strong drug-event causal associations[1]
  - severe unexpected adverse events[2]
- *Fosters suspicions ® prompts further warranted investigation[2]*


1. Tubert P, et al. J Clin Epidemiol, 1992
2. Alvarez-Requejo A et al. Eur J. Clin Pharmacol, 1998.
3. Goldman S. Clinical Therapeutics, 1998.

# Spontaneous AE Reporting

**Limitations**

- **Underreporting**
  - **< 10% SAE's; < 4% AE's are reported**
  - **precipitous decline in reporting after 2nd post-marketing year**
- **Confounders / Biases**
  - **reporting environment**
  - **quality of data**
    - **numerator / denominator inaccuracies**
    - **temporally-associated clinical and lab data**
    - **challenge /re-challenge information**
    - **outcome**

**Goldman S, 1998**
**Talbot JCC and Nilsson BS, 1998**

# Pharmacosurveillance Alternative

- **Post licensure randomized clinical trials**
  - industry-sponsored
  - larger subject accrual than pre-licensure study
  - very expensive if to GCP specs

- **Post-marketing cohort studies**
  - industry-sponsored
  - slow recruitment / lack of control arm

- *** Long-term global pharmacosurveillance programs**
  - industry-sponsored, or
  - independent of / supported by industry
  - facilitated by regulatory harmonization

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# Workshop on FVIII Inhibitors in PTP's

## The Question: Host or Product?

**Post-Licensure Pharmacosurveillance**

- Assuming the need for a long-term pharmacosurveillance program, what are its necessary elements with respect to:
  - project scope
    - HTC / government agency / industry participation?
    - type of data collection?
    - surveillance period
  - clinical / laboratory data collection / analysis / reporting
    - national vs. international databases?

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# Workshop on FVIII Inhibitors in PTP's

## The Question: Host or Product?

**Post-Licensure Pharmaco-Surveillance (cont'd)**

- Role of physician organizations? Government agencies? Industry?
- Funding?

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# Proposed PS Program

## Participation

- Universal data collection system for all FVIII products

| Products globally distributed | Products with limited distribution |
|---|---|
| ↓ | ↓ |
| International Database | National / Multinational Database |

- Hemophilia treater-driven*

* Vermylen and Briet, Lancet 1993

# Proposed PS Program

## Subject Selection

- PTP's
  - defined by pre-licensure clinical trials
  - on all factor VIII products
    - plasma-derived
    - recombinant
    - future modified products
- Observation period defined by cumulative factor VIII exposure days, not time

# Proposed PS Program

## Data Set (1)

- **Minimum Data Set**
  - **Defined by:** Regulatory agencies with industry input
  - **Focus:** Ascertain product immunogenicity
    - incidence / prevalence of HT / LT inh
    - at risk PTP population
    - risk period
    - outcomes
  - **Goal:** Ongoing reassessment of product risk / benefit ratio

# Proposed PS Program

## Data Set (2)

- **Minimum Data Set**
  - Tools
    - Adequately powered cohort size and observation period
    - Reliable database for numerator[#] / denominator[*] ascertainment
      - [#] clinician participation / adherence to protocol
      - [*] industry-supported factor distribution data
    - Strict definitions of
      - PTP with / without previous inhibitor
      - Inhibitor (HT / LT)
        - standardized assay (? centralized)
        - sensitivity / specifically criteria
        - inclusion of recovery / survival data?
      - Frequency of monitoring
      - Outcomes

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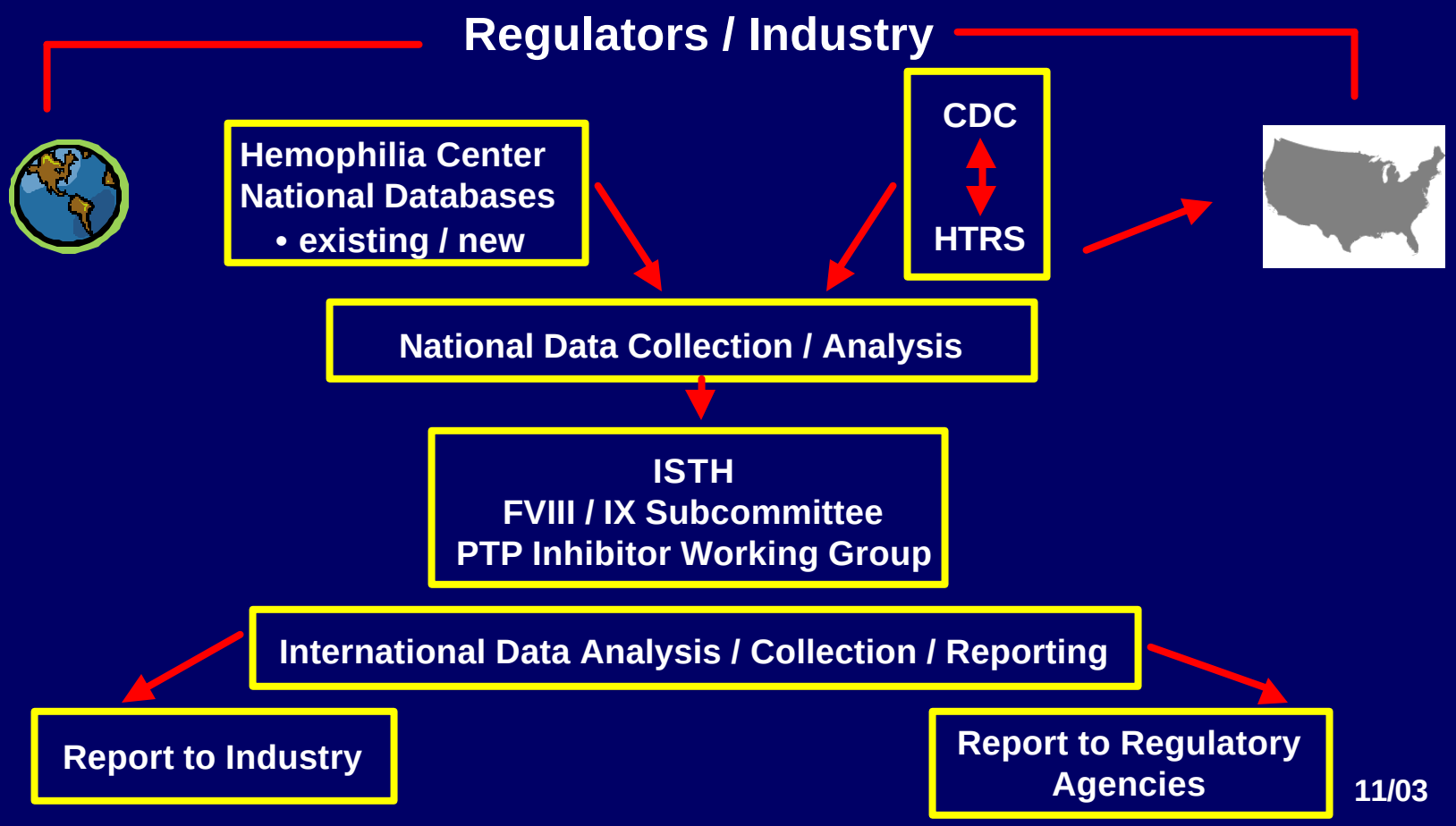
# Proposed PS Program

## MDS Collection / Analysis / Reporting



# Proposed PS Program / Funding

## MDS Collection / Analysis / Reporting

Hemophilia Center
National Databases
• existing / new

CDC
HTRS

National Data Collection / Analysis

Industry
National Org.
Gov't / Private Funds

ISTH
FVIII / IX Subcommittee
PTP Inhibitor Working Group

International Data Analysis / Collection / Reporting

Report to Industry

Report to Regulatory Agencies

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# Proposed PS Program

## Data Set (3)

- **Comprehensive Data Set**

  - **Defined by:** Clinical investigators / scientists
  - **Focus:** Ascertain role of host and host / treatment interaction in PTP inhibitor formation
    - host hemophilia / immunologic genotype / phenotype
    - pertinent non-product-related inhibitor risk factors
    - type of hemorrhage / treatment specifics
    - anti-FVIII antibody characterization

# Proposed PS Program

## Data Set (4)

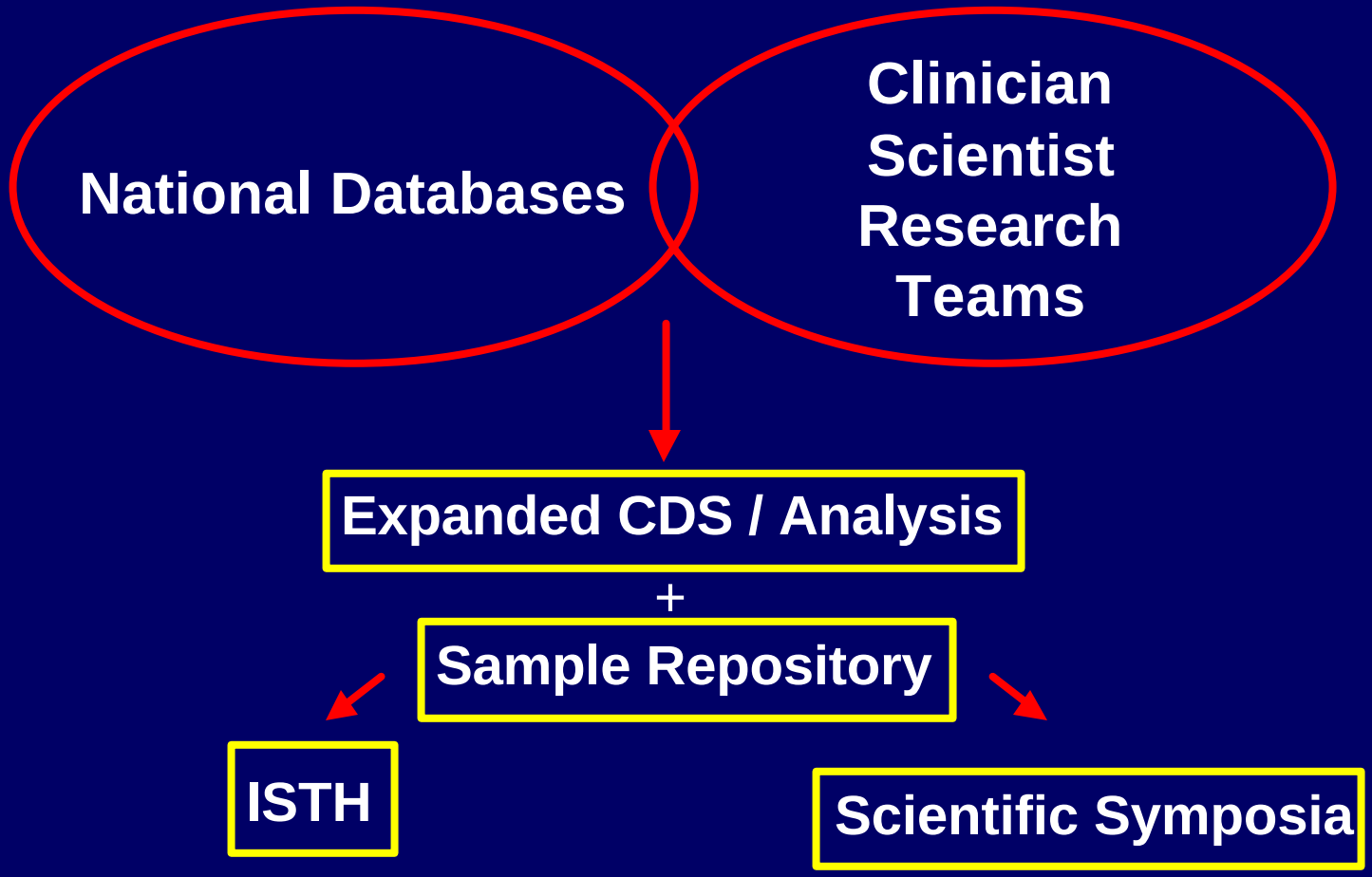
- **Comprehensive Data Set**

  - **Tools**

    - **Adequately powered cohort size and observation period (case controls?)**
    - **Comprehensive clinical database**
    - **Prospective / retrospective sample collection / repository**

# Proposed PS Program

**Comprehensive Data Collection / Analysis / Reporting**

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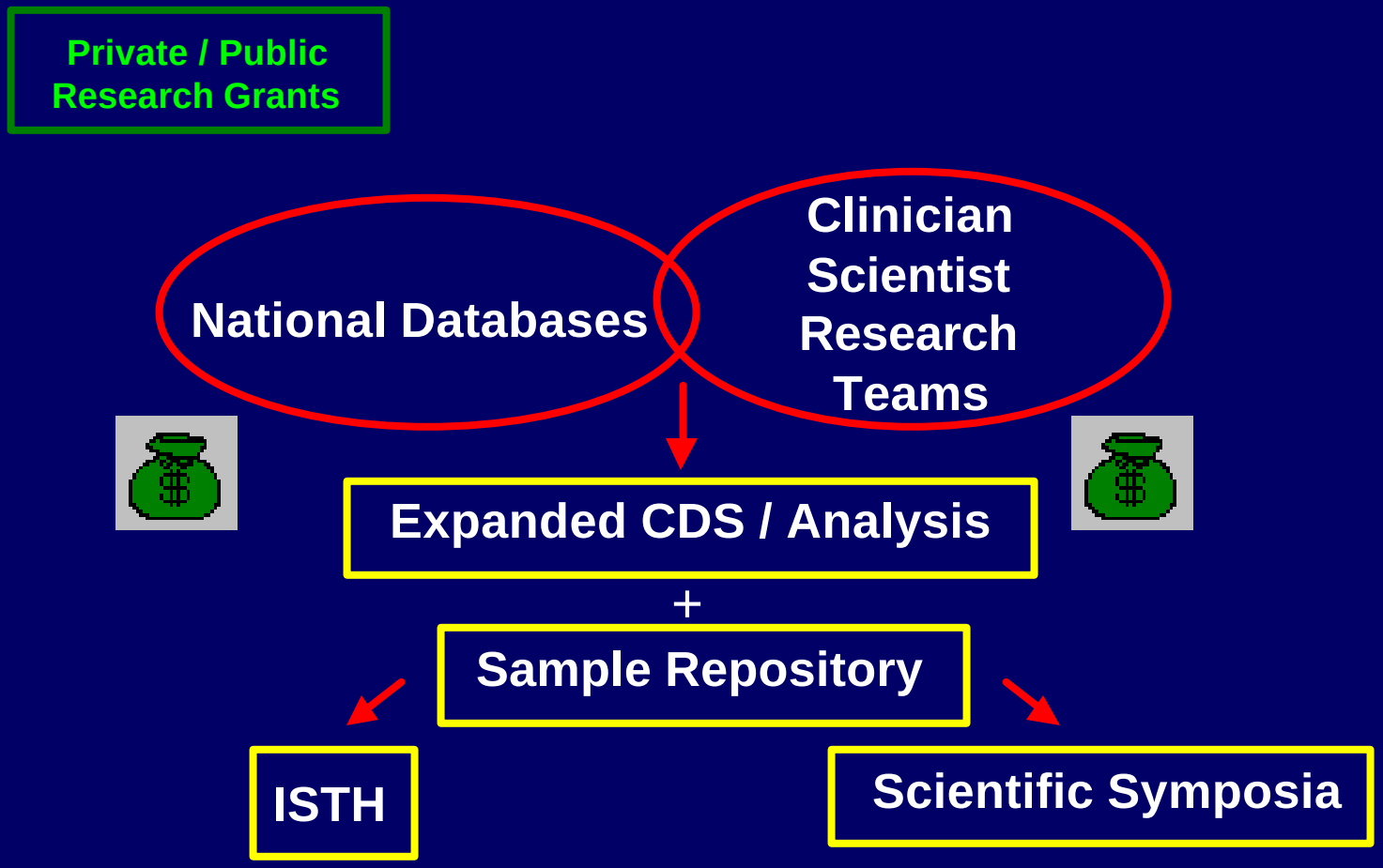
# Proposed PS Program / Funding

## Comprehensive Collection / Analysis / Reporting

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# Workshop on FVIII Inhibitors in PTP's

## Where to Go From Here

**Moving forward**

- **Panel Discussion**
- **Crucial Decisions**